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The first brain: species comparisons and evolutionary implications for the enteric
and central nervous systems

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Abstract

Background: The enteric nervous system (ENS) and the central nervous system (CNS) of mammals both contain integrative neural circuitry and similarities between them have led to the ENS being described as the brain in the gut. Here we explore relationships between the ENS and CNS across the animal kingdom.

Results: An ENS occurs in all animals investigated, including hydra, echinoderms and hemichordates that do not have a CNS. The general form of the ENS, which consists of plexuses of neurons intrinsic to the gut wall and an innervation that controls muscle movements, is similar in species as varied and as far apart as hydra, sea cucumbers, annelid worms, octopus and humans. Moreover, neurochemical similarities across phyla imply a common origin of the ENS. Investigation of extant species suggests that the ENS developed in animals that preceded the division that led to cnidaria (exemplified by hydra) and bilateria, which includes the vertebrates. The CNS is deduced to be a bilaterian development, later than the divergence from cnidaria. Consistent with the ENS having developed independent of the CNS, reciprocal connections between ENS and CNS occur in mammals, and separate neurons of ENS and CNS origin converge on visceral organs and prevertebral ganglia.

Conclusion: The ENS arose before and independently of the CNS. Thus the ENS can be regarded as the first brain.

KEYWORDS

Enteric nervous system, central nervous system, evolution, neurotransmitters, serotonin

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Key Points

- All extant animal species that have neurons have an enteric nervous system (ENS), including those species that can be traced back the furthest in evolutionary terms. However, not all animals have a central nervous system (CNS).
- An ENS with similar features occurs in cnidaria and bilateria (both protostomes and deuterostomes), but a CNS occurs only in bilateria, although not in all bilateral animals.
- In mammals, the ENS and CNS have reciprocal and convergent connections.
- It is concluded that the ENS evolved earlier than the CNS and that once both had developed they formed connections with each other and convergent connections with other organs.

1. INTRODUCTION

The enteric nervous system (ENS) is unlike any other peripheral part of the nervous system. It contains complete circuits for reflex control of the digestive tract that can operate even in a segment of intestine that is removed from an animal, and from which all vestiges of CNS connections have been removed.^{1,2} Deeper investigation has revealed intrinsic nerve circuits that include intrinsic sensory (primary afferent) neurons, interneurons and several classes of motor neuron.³⁻⁵ Moreover, the microstructure of enteric ganglia is more similar to the central nervous system (CNS) than to other peripheral ganglia.^{4,6} For these reasons it has been likened to a second brain. In this brief review, we compare the ENS and the neural control of digestion in different animals, which leads us to the conclusion that the ENS arose prior to the CNS. It has maintained its general form throughout evolution, suggesting a degree of conservation of the ancient ENS. Moreover, the nature of reciprocal connections between ENS and CNS suggests a co-evolution of interdependent, rather than derivative, nervous systems.

2. COMPARISONS OF THE ENTERIC NERVOUS SYSTEM BETWEEN ANIMALS AND IMPLICATIONS FOR ITS EVOLUTION

The digestive system of the animal with the most ancient antecedent is probably that of the sponge. Sponges have holes or spaces through which water bearing nutrients flows; these are the first recognisable animal digestive systems.⁷ Although there is evidence for motility within the digestive tubes, particularly movement of the flagella of choanocytes, which pushes water through the tubes, sponges have no nervous system. The animals with a nervous system whose form can be traced back furthest are cnidarians, exemplified by the genus *Hydra*, which evolved approximately 650 million years before present (bp). The hydra is a sessile tubular animal with an opening to the water in which it lives, and an internal epithelial lining that separates the nutrients within the gut tube from the body tissues. The cnidarian ENS is distributed as several hundreds of neurons that

form a mesh-work within the wall of the gut tube, but there is no evidence of the formation of specialised aggregations of neurons (head ganglia) that might be a first stage of brain formation.⁸⁻¹⁰ The body wall of hydra has longitudinal and circular muscle layers to which the ENS is closely related.^{11, 12} The neuronal plexus extends into the tentacles that sweep water and nutrients into the gut tube. The cnidarian nervous system is often described as a nerve net, but it in fact consists of individual neurons that contain transmitters including catecholamines, 5-HT and neuropeptides, with synaptic specialisations between the neurons.^{13, 14}

Hydra can be rendered nerve free by treatment with colchicine.¹⁵ New animals that bud and develop from the colchicine-treated hydra are bereft of neurons. These derivative animals have both no neurons and no exposure to colchicine. They cannot feed, but can be kept alive by placing freshly killed *Artemia* into the body cavity using a fine pipette. Nerve-free hydra exhibit only weak movements; neurons must be intact for adequate peristaltic movements of the gut tube to occur.¹² Propulsive and mixing movements are observed in normal hydra in response to nutrients, but not non-nutrients that are placed within the hydra body cavity. Thus it can be deduced that hydra have nutrient detectors and that neurons of the hydra ENS react to the introduction of food and direct motor outputs to produce peristaltic movements.¹² Thus, as in mammals, the ENS of hydra has sensory and motor neuron functions, which, given that the hydra ENS contains synaptically connected neurons, suggests that there may be separate sensory and motor neurons, and perhaps interneurons. In normal hydra after food has been digested (6-9 hours after feeding), circumferential and longitudinal movement of the body wall expels the residuum (cnidarian feces) into the environment. This suggests that directly or indirectly the hydra ENS detects products of digestion or the decline in nutrient concentration. Thus the cnidarian ENS, like the mammalian ENS, is programmed to direct a range of movements: peristalsis, mixing movements and expulsion. Lack of an ENS is incompatible with life in this most primitive of animals that has a nervous system, as it is in humans, who cannot survive the congenital lack of an ENS in Hirschsprung disease, in which no propulsive activity occurs in the aganglionic region of bowel, or when later ENS loss occurs in Chagas' disease.¹⁶

Other invertebrates, including echinoderms,¹⁷ acorn worms,¹⁸ cephalopods,¹⁹ gastropod molluscs^{20, 21} and annelid worms²² have an ENS (Table 1), some of which have architectures reminiscent of that of vertebrates, including human (Fig. 1). However, the ENS of insects has diverged from that of other invertebrates, in that enteric neurons are in ganglia and along nerve strands on the surface of the gut, rather than being embedded in its wall.^{23, 24} In snails^{25, 26} two layers of ganglia, identified as myenteric and submucosal ganglia, as is observed in other invertebrates and in mammals (Fig 1), have been described. Nerve tracing studies indicate that

ganglionic clusters of molluscs, including the stomatogastric ganglia, project axons to the digestive tube, perhaps making connections with enteric neurons.²⁷

The chemistries of invertebrate enteric neurons, and by implication, the chemistries of their neurotransmitters, exhibit some similarities and also major differences from vertebrates.²⁸ In particular, typical invertebrate peptides, which are not found in vertebrates or whose sequences are remote from those of their vertebrate relatives, occur in the invertebrate ENS. These include the molluscan peptide, FMRFamide, the insect peptide family, the adipokinetic hormones, and the invertebrate tachykinin-related peptides (the locustakinins). A mammalian enteric neurotransmitter, serotonin, occurs in the invertebrate ENS of a wide range of species, including hydra, acorn worms and insects.^{13, 18, 29} Within the vertebrates, the innervation of the gastrointestinal tract and the architecture of the ENS are similar, and primary neurotransmitters are well preserved.^{30, 31} Thus the form and function of the ENS has persisted, but between vertebrates and invertebrates there has been some divergence of the chemical messengers through which the neurons communicate.

3. RECIPROCAL AND CONVERGENT CONNECTIONS OF THE ENS AND CNS

The ENS has outwardly projecting neurons, that, like those of the CNS, influence the functions of their targets. In this sense, the CNS and ENS mirror each other, both giving rise to efferent pathways and both receiving afferent input. Both also contain intrinsic integrative circuitry. Peripheral organs other than the gut are connected with the CNS through efferent control pathways that emanate from the CNS and through primary afferent neurons with cell bodies in dorsal root and cranial ganglia close to the CNS, such as the trigeminal, nodose and jugular ganglia.

A striking feature of the ENS is the existence of neurons with cell bodies in enteric ganglia that project to the CNS. These include entero-bulbar neurons with cell bodies in the stomach and proximal duodenum that project to the lower brain stem³² and neurons that project from the rectum to the lumbo-sacral spinal cord.^{33, 34} The recto-spinal neurons have typical enteric neuron, type I morphology and receive synapses, presumably from other enteric neurons. The cell bodies of gastro-bulbar and duodeno-bulbar neurons are contacted by vagal efferent neurons with cell bodies in the lower brain stem.³² Thus there exist reciprocal outwardly directed pathways from the ENS to CNS and CNS to ENS (Fig. 2).

Other projections that are peculiar to the ENS are the intestinofugal pathways, in which neurons with cell bodies in the intestine innervate the trachea, gall-bladder, pancreas and the cell bodies of sympathetic post-ganglionic neurons within prevertebral ganglia (Fig. 2). The axons of intestinofugal neurons that project to prevertebral ganglia converge on neurons that also receive synaptic input from the CNS.³⁵ These intestinofugal neurons are parts of the afferent limbs of entero-enteric reflexes, through which one region of intestine causes inhibition of other, generally

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more proximal, regions.^{36, 37} These peripheral reflexes that pass through abdominal sympathetic ganglia usually remain unmentioned in text-books. Nevertheless, the existence of such reflex pathways is well established.

The first evidence for intestinofugal neurons was the observation that a proportion of synaptic contacts in the celiac ganglion remained intact after the connections of the ganglion with the CNS had been severed and sufficient time (21 days) was allowed for the disconnected endings of neurons to degenerate.³⁸ To probe the physiological significance of the pathways, Kuntz³⁹ prepared cats in which the inferior mesenteric ganglia were decentralized and the colon remained connected, but was divided, thus preventing connections through intramural pathways. Distention of the distal segment with a balloon inhibited contractions in the proximal segment. The only possible pathway for these reflexes was through the inferior mesenteric ganglia. In the 77 years following Kuntz's observations, there has been a steady accumulation of confirmatory data that has provided greater detail about the intestinofugal neurons and the reflex pathways to which they contribute.³⁷

Experiments in which segments of intestine and their connected sympathetic postganglionic neurons have been studied in isolation, e.g.^{40, 41}, show that the intestinofugal neurons are activated by distension and, when active, provide excitatory synaptic inputs to sympathetic postganglionic neurons. Experiments to investigate whether the intestinofugal neurons are themselves mechanosensitive, or whether they receive inputs from neurons in the intestinal wall indicate that the intestinofugal neurons can be both directly activated by mechanical forces, and activated through enteric neurons that synapse with them.⁴¹⁻⁴³ The consensus from physiological studies is that entero-enteric reflexes through prevertebral ganglia carry signals from more distal to more proximal regions of the digestive tract and they regulate the passage of material in a proximal to distal direction.

Other intestinofugal neurons whose axons arise from the ENS project to the pancreas⁴⁴ the biliary system^{45, 46} and the airways.⁴⁷ The functions of these connections have been little explored, but they are presumably involved in co-ordinating the activities of these organs.

Central autonomic control of peripheral organs, except for the gut, involves motor pathways from the CNS that innervate final effector tissues, most commonly smooth muscle and glands. However, the pathways from the CNS to the gastrointestinal tract in most cases impinge on enteric neurons.¹⁶ Furthermore, if the enteric neurons are congenitally absent, for example in colorectal aganglionosis, the extrinsic innervation that reaches the gut is disorganized.⁴⁸ This may suggest that the ENS was formed before it became a target for CNS projections.

4. DID AN ANCIENT NERVOUS SYSTEM LEAD TO THE ENS IN CNIDARIA AND THE ENS AND CNS IN BILATERIA?

One of the remarkable observations is that neurotransmitters of cnidarians, which have an ENS but not a CNS, occur in the ENS and the CNS of bilateria, including mammals. These include nitric oxide,⁴⁹ 5-HT,¹³ and oxytocin/vasopressin-like peptides.^{11, 12} Transcription factors involved in neurogenesis and neural cell type specification are also conserved between cnidaria and vertebrates.⁵⁰ This suggests that the antecedents of the ENS of cnidarians and the ENS and CNS of bilateria derived from a metazoan ancestor common to both groups. On the other hand, in extant mammals, some of the neurotransmitters that are prominent in the CNS, such as glutamate, dopamine, gamma-aminobutyric acid and serotonin, have only minor roles in the ENS.¹⁶ In the case of serotonin, it is controversial whether it has a significant role in the ENS of mammals.^{51, 52}

Previous considerations of the evolutionary origins of the CNS suggest that it arose in the common ancestors of the bilateria, urbilateria,⁵³ even though it is generally agreed that the some deuterostomes (echinoderms and hemichordates) cannot be said to have a CNS⁵⁴ (Table 1). If the conservation of neurotransmitter systems is taken into account, as well as similarities in neuronal and synaptic morphologies between cnidarian and other invertebrate and vertebrate nervous systems,¹³ an earlier development of a nervous system than in urbilateria can be proposed to have occurred in ‘ureumetazoa’, postulated ancestors of both cnidarians and bilateria.⁵⁰ This would place the ureumetazoan ENS as a likely precursor of both the modern ENS and the CNS. Our theory of the ENS as the ‘first brain’ is consistent with the ENS and CNS of mammals both having afferent and efferent connections with other organs, and having reciprocal connections with each other. Although the first brain hypothesis that we have advanced is consistent with current knowledge of the nervous systems of a wide range of animals, further studies, particularly of under-investigated invertebrates, would be of significant value in understanding the evolution of the ENS.

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COMPETING INTERESTS

The authors have no competing interests.

AUTHOR CONTRIBUTION

JBF and MJS researched the literature and wrote the manuscript

Table 1

Bilateria	Cnidaria
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	Protostomes		Deuterostomes					
	Insects	Annelids	Echinoderms	Hemichordates	Amphioxys	Ascidians	Vertebrates	Hydra
CNS	Ventral	Ventral	None	None	Dorsal	Dorsal	Dorsal	None
ENS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table 1: The presence or absence of a central nervous system (CNS) and/or enteric nervous system (ENS) in different animal groups. The presence of an ENS in extant cnidaria, hemichordates and echinoderms, animals without a CNS, suggests that the ENS existed in the common ancestors of cnidarian and bilateria. On the other hand, the presence of a CNS only in some bilateria suggests that it developed subsequent to divergence from cnidaria. It might have not developed, or regressed in echinoderms and hemichordates.

Figure Descriptions

Fig 1 Comparison of the ENS of a hydra and of an echinoderm, animals that do not have a CNS, with human and octopus, both of which have a CNS. Each diagram represents the gut wall in transverse section, with nerve cell bodies in red and their processes in black. In each of the four species there is an enteric nervous system that provides innervation of the muscle of the gut wall. There is detailed knowledge of the projections and connections of enteric neurons in human and other mammals, but not in the other animals illustrated here. For details see: hydra, Grimmelikhuijzen et al.^{11, 55}; echinoderm, García-Arrarás et al.¹⁷; octopus, Alexandrowicz¹⁹; human and other mammals, Furness¹⁶. It is not certain whether the innervation of the circular muscle in echinoderms comes from the serosal or submucosal ganglia.

Fig 2: Reciprocal ENS-CNS connections. Neurons project away from both the ENS (enterofugal neurons, red) and the CNS (centrifugal neurons, blue). These form reciprocal connections between the ENS and CNS, and convergent pathways that innervate the trachea, gall bladder, pancreas and sympathetic prevertebral ganglia.

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Hydra

Echinoderm

Human

Octopus

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